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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/691,123	10/22/2003	Stephen J. Brand	24492-011	5348

30623 7590 09/15/2006

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EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 09/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/691,123	BRAND ET AL.	
	Examiner	Art Unit	
	Marcela M. Cordero Garcia	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7-10,12-14,24-26,33-45,101-107 and 110* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-10,12-14,24-26,33-45,101-107 and 110* is/are rejected.

7)☒ Claim(s) *7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/04 and 07/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election of Group I (drawn to claims 1-4, 7-10, 12-14, 24-26, 33-45, 101-107 and 110) and of the species: Glucagon 1-like peptide receptor ligand (GLP-1) as the FACGINT, gastrin as the gastrin/CCK receptor ligand and rapamycin as the immunosuppressive agent in the reply filed on June 21, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Information Disclosure Statement

The information disclosure statements (IDSs) submitted on 2/25/04 and 7/25/06 were filed after the mailing date of the application on 10/22/03. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. In addition, there seems to be an extra disclosure statement dated 2/25/06, which was not considered because a copy was not available to the Examiner. Please provide a copy for consideration by Examiner if this IDS was indeed submitted.

Claim Objections

Claim 7 objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 7, as amended, does not properly depend on any claim, i.e., "The method according to claim, wherein". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 7-10, 12-14, 24-26, 33-45, 101-107 and 110 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the species gastrin and GLP-1, does not reasonably provide enablement for the plethora of compounds encompassed by all gastrin/CCK receptor ligands and for any and all factors coined as FACGINT (factor for complementing gastrin for islet neogenesis therapy) which encompass glucagon-like peptide 2 receptor ligands, gastric inhibitory polypeptide (GIP) receptor ligands, keratinocyte growth factor (KGF) receptor ligands, dipeptidyl peptidase IV inhibitors, REG protein receptor ligands, Growth hormone receptor ligands, Prolactin (PRL) receptor ligands, Insulin-like Growth Factor (IGF) receptor ligands, PTHrP receptor ligands, fibroblast growth factor (FGF) receptor ligands, hepatocyte growth factor (HGF) receptor ligands, bone morphogenetic protein (BMP) receptor ligands, a transforming growth factor-b (TGF-b) receptor ligands; laminin receptor ligands; vasoactive instestinal peptide (VIP) receptor ligands; fibroblast receptor ligands, keratinocyte growth factor receptor ligands, nerve

growth factor (NGF) receptor ligands, vascular endothelial growth factor (VEGF) receptor ligands, erythropoietin (EPO) receptor ligands, pituitary adenylate cyclase activating polypeptide (PACAP) receptor ligands, granulocyte colony stimulating factor (G-CSF) receptor ligands, granulocyte-macrophage colony stimulating factor (GM-CSF) receptor ligands, platelet-derived growth factor (PDGF) receptor ligands and secretin receptor ligands. In addition, for each of the receptor ligands above, all known analogues, variants and derivatives whether naturally occurring or made by mutagenesis or designed and synthesized are considered equivalent to that 'FACGINT' (e.g., disclosure, pages 14 and 15 lines 1-10). With regards to the gastrin/CCK receptor ligands, the term "encompasses any compound that binds to, interacts with or stimulates the gastrin/CCK receptor" and encompasses peptide and non-peptide agonists (e.g., page 19, lines 28-31 and page 20, lines 1-18). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

With regards to the effect of amino acid substitution in a peptide or protein, the art is unpredictable.

Rudinger (J. Rudinger. In: Peptide Hormones, JA Parsons, Ed. (1976) 1-7) teaches that, "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted a priori but must be determined from case to case by painstaking experimental study." (Page 6).

SIGMA (SIGMA. Designing Custom Peptides. http://www.sigma-genosys.com/peptide_design.asp (Accessed 12/16/2004), 2 pages) states that with regards to design of peptide sequences that, "Even for relatively short sequences, there are essential and non-essential (or less important) amino acid residues, although the relative importance of the individual amino acid residues is not always easy to determine." (Page 1). SIGMA further describes what effect some substitutions may have, rather than what effect they will have on hydrophobicity, secondary structure (which will affect tertiary and quaternary structure), and solubility.

With regards to prediction of the native conformation of a protein (structure), the art is unpredictable.

Berendsen (H..J.C. Berendsen. A Glimpse of the Holy Grail? Science (1998) 282, pages 642-643) states, "The prediction of the native conformation of a protein of known amino acid sequence is one of the great open questions in molecular biology and one of the most demanding challenges in the new field of bioinformatics." (Page 642). Berendsen states that, "Folding to the stable native state [computationally] has not (yet) occurred, and the simulations do not contain any relevant statistics on the process. The real protein will fold and refold hundreds to thousands of times until it stumbles into the stable conformation with the lowest free energy. Because this hasn't happened (and couldn't happen) in the simulations, we still cannot be sure of the full adequacy of the force field. (Page 642).

Further, the effects of a single amino acid substitution can have substantial effects on proteins in structure and/or function and are exemplified by the difference between hemoglobin (Hb) and abnormal hemoglobins, such as sickle-cell hemoglobin (HbS). VOET (D. Voet and J.G. Voet. Biochemistry, 2nd Edition.(1995), pages 235-241) teaches that the mutant hemoglobin HbE [Glu B8(26)β → Lys] has, "no clinical manifestations in either heterozygotes or homozygotes." (Page 235). Further, Hb Boston and Hb Milwaukee both have single point mutations which result in altered binding affinity and ineffective transfer from the Fe(III) to Fe(II) oxidation state. Conversely, a single point mutation in Hb Yakima results in increased oxygen binding by the heme core, and in Hb Kansas, the mutation causes the heme center to remain in the T state upon binding oxygen (rather than structurally rearranging to the R state). (Page 236).

HbS is a single point mutation, Val → Glu A3(6)β (Page 236), which results in deformation and rigidity of the red blood cell. The mutation also provides protection against most malarial strains.

Further, Smilek (D.E. Smilek, et al. Proc. Natl. Acad. Sci. USA (1991) 88, pages 9633-9637) teaches that a single amino acid substitution in the myelin basic protein peptide, "confers the capacity to prevent rather than induce EAE even after peptide-specific encephalitogenic T-cells have been activated." (Abstract).

Messer (W.S. Messer, "Vasopressin and Oxytocin", web document updated 4/3/2000;

http://www.neurosci.pharm.utoledo.edu/MBC3320/vasopressin.htm; 5 pages) that two compounds, vasopressin [cyclo(1-6)CYIQNCPLG-NH_2] and oxytocin [cyclo(1-6)CYFQNCPRG-NH_2] differ by only two amino acids, as indicated, yet they have different functions. Vasopressin (antidiuretic hormone, ADH), "at low doses controls the resorption of water by the distal tubules of the kidneys and regulates the osmotic content of blood... [and at] high doses, ADH causes contraction of arteriles (sic) and capillaries, especially those of the coronary vessels, to produce localized increases in blood pressure." (page 1).

Oxytocin, on the other hand, stimulates smooth muscle contraction in the uterus, mammary glands, and the "alveoli and larger sinuses of the mammary glands to make readily available milk" (page 1).

Further, ADH has 2 types of receptors (V1 and V2) found in vascular smooth muscle and the kidney, while oxytocin has one type of receptor found in uterine and mammary smooth muscle.

Given that one could not determine the structure of a protein computationally, and that the effect of amino acid substitution is highly unpredictable, and can produce an effect opposite or different to that which is desired, it flows logically that one would be unduly burdened with experimentation to determine the effect of amino acid substitution(s), derivatization(s), deletion(s) in the plethora of receptor ligands instantly claimed, with regards to structure, function, or physical/chemical properties. Additionally, obtaining and testing the full scope of the non-peptidic agonists of FACGINT

and/or gastrin/CCK receptor ligands as defined in the specification would also require undue experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 13-14 and 24 rejected under 35 U.S.C. 102(b) and under 102(e) as being anticipated by Ramiya et al. (US 2002/0182728).

Sheridan teaches a method for inducing pancreatic islet neogenesis in a mammal, the method comprising administering to the mammal a composition

comprising a combination of a FACGINT (i.e., GLP-1) and a gastrin/CCK receptor ligand (i.e., gastrin) in an amount sufficient to increase proliferation of islet precursor cells in pancreatic tissue, thereby inducing islet neogenesis (e.g., claims 1, 5, 12-15).

Therefore, the reference is deemed to anticipate the instant claims above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 7-10, 12-14, 24-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Parikh et al. (US 6,558,952) in view of Hoffman (US 6,358,924).

Parikh et al. teaches a method of treating diabetes by administering to the individual in need thereof a composition including a gastrin (e.g., abstract, column 6, lines 10-18, 26-34 and 45-56, column 8, lines 30-53).

Parikh et al. do not teach a method of treating diabetes administering a FACGINT such as GLP-1.

Hoffman teaches a method of treating diabetes by administering to the individual in need thereof a composition including GLP-1 (column 1, lines 20-37, column 2, lines 19-22, claims 1 and 11).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the instant compounds (i.e., gastrin and GLP-1) for their known benefit since each is well known in the art for the treatment of diabetes. Applicants invention is predicated on an unexpected result, which typically involves synergism, an unpredictable phenomenon, highly dependent upon specific proportions and/or amounts of particular ingredients. Any mixture of the components embraced by the claims which does not exhibit an unexpected result (e.g., synergism) is therefore ipso facto unpatentable.

Accordingly, the instant claims, in the range of proportions where no unexpected results are observed, would have been obvious to one of ordinary skill having the above cited references before him.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. The adjustment of particular conventional working conditions [e.g., determining appropriate administration methods and/or dosages

(e.g., Parikh et al., e.g., column 8, lines 30-53, columns 9-11) within such therapeutic method] is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan. Thus the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1, 33-35, 39-45 and 104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Parikh et al. (US 6,558,952) in view of Hoffman (US 6,358,924) and in view of Baeder et al. (EP 0 507 555 A1).

Parikh et al. and Hoffman are relied upon as above.

Baeder et al. teach a method for treating diabetes by administrating rapamycin.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the instant compounds (i.e., gastrin, GLP-1 and rapamycin) for their known benefit since each is well known in the art for the treatment of diabetes. This rejection is based on the well established proposition of patent law that no invention resides in combining old ingredients of known properties where the results obtained thereby are no more than the additive effect of the ingredients, In re Sussman, 1943 C.D. 518. Applicants invention is predicated on an unexpected result, which typically involves synergism, an unpredictable phenomenon, highly dependent upon specific proportions and/or amounts of particular ingredients. Any mixture of the

components embraced by the claims which does not exhibit an unexpected result (e.g., synergism) is therefore ipso facto unpatentable.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. The adjustment of particular conventional working conditions [e.g., determining the mode of administration within such therapeutic method, e.g., Parikh et al. column 8, lines 30-53; Baeder, e.g., claims)] is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan.

Thus the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an

invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 7-10, 12-14, 24-26, provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 13, 21, 32, 91-92 and 101 of copending Application No. 10/532,295 (e.g., pages 4-5). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both drawn to a method of treating diabetes administering a gastrin/CCK receptor ligand and a FACGINT such as GLP-1. Further, the instantly claimed method encompasses and/or is encompassed by the claimed method of Application '295.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcela M. Cordero Garcia whose telephone

number is (571) 272-2939. The examiner can normally be reached on M-Th 7:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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MMCG 09/01